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L14: Entry 1 of 1 File: USPT Feb 13, 2001

DOCUMENT-IDENTIFIER: US 6187304 B1
TITLE: Effects of IFN-.gamma. on cardiac hypertrophy

Brief Summary Text (18):
At present, the treatment of cardiac hypertrophy varies depending on the underlying cardiac disease. Catecholamines, adrenocorticosteroids, angiotensin, prostaglandins, leukemia inhibitory factor (LIF), endothelin (including endothelin-1, -2, and -3 and big endothelin), cardiotrophin-1 (CT-1) and cardiac hypertrophy factor (CHF) are among the factors identified as potential mediators of hypertrophy.

Detailed Description Text (39):
Stable liquid pharmaceutical compositions comprising an effective amount of non-lyophilized IFN-.gamma. along with a buffer capable of maintaining the pH at 4.0-6.0, a stabilizing agent, and a non-ionic detergent are disclosed in U.S. Pat. No.5,151,265 issued Sep. 29, 1992. The stabilizing agent typically is a polyhydric sugar alcohol, such as mannitol, and the non-ionic detergent may be a surfactant, e.g. polysorbate 80 or polysorbate 20. The non-ionic detergent preferably is present in a range of about 0.07 to 0.2 mg/ml, and most preferably in a concentration of about 0.1 mg/ml. Suitable buffers are conventional buffers of organic acids and salt thereof, such as nitrate buffers (e.g., monosodium citrate-disodium citrate mixture, citric acid-trisodium citrate mixture, citric acid-monosodium citrate mixture, etc.), succinate buffers (e.g., succinic acid-monosodium succinate mixture, succinic acid-sodium hydroxide mixture, succinic acid-disodium succinate mixture, etc.), tartarate buffers (e.g., tartaric acid-sodium tartarate mixture, tartaric acid-potassium tartarate mixture, tartaric acid-sodium hydroxide mixture, etc.), fumarate buffers (e.g. fumaric acid-monosodium fumarate mixture, fumaric acid-disodium fumarate mixture, monosodium fumarate-disodium fumarate mixture, etc.), gluconate buffers (e.g. gluconic acid-sodium gluconate mixture, gluconic acid-sodium hydroxide mixture, gluconic acid-potassium gluconate mixture, etc.), oxalate buffers (e.g., oxalic acid-sodium oxalate mixture, oxalic acid-sodium hydroxide mixture, oxalic acid-potassium oxalate mixture, etc.), lactate buffers (e.g. lactic acid-sodium lactate mixture, lactic acid-sodium hydroxide mixture, lactic acid-potassium lactate mixture, etc.), and acetate buffers (e.g., acetic acid-sodium acetate mixture, acetic acid-sodium hydroxide mixture, etc.)

Other Reference Publication (18):
Kurzrock et al., "LIF: Not Just a Leukemia Inhibitory Factor" Endocrine Reviews 12(3):208-217 (1991).

Other Reference Publication (21):
Metcalf, "Leukemia Inhibitory Factor--A Puzzling Polyfunctional Regulator" Growth Factors 7:169-173 (1992).

End of Result Set

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L22: Entry 11 of 11 File: USPT Dec 3, 1996

DOCUMENT-IDENTIFIER: US 5580856 A
TITLE: Formulation of a reconstituted protein, and method and kit for the production thereof

DATE FILED (1):
19940715

Detailed Description Text (12):
The present invention may suitably be applied to any protein subjected to freeze-drying or other forms of drying such as spray-drying and air drying. Exemplary proteins for use in the present invention include, but are not limited to, growth factors, hormones, enzymes, clotting factors, structural proteins, complement factors, antibodies and antigens; pesticides (e.g., herbicides and fungicides) and bacterial toxins. Specifically, such proteins include Erythropoietin; Granulocyte Colony Stimulating Factor; Granulocyte Macrophage Colony Stimulating Factor; Epidermal Growth Factor; Acidic Fibroblast Growth Factor; Basic Fibroblast Growth Factor; Keratinocyte Growth Factor; Interferon-alpha; Interferon-gamma; Interleukins (IL alpha, IL-1 beta, IL-2, IL-3, IL-4, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11); Factor VIII; Antithrombin III; Insulin; Tumor Necrosis Factor-alpha; Tumor Necrosis Factor-beta; Transforming Growth Factor-beta; Tissue Plasminogen Activator; Platelet-derived Growth Factor; Urokinase; Streptokinase; Peroxidase; RNA Polymerase; T7 DNA Polymerase; Taq DNA polymerase; Fibrinogen; Thrombin; Alcohol dehydrogenase; Alkaline phosphatase; Arginase; Ascorbate oxidase; Cholesterol esterase; Cholinesterase; Collagenase; DNase I; DNase II; Enterokinase; Glucose-6-phosphate dehydrogenase; Glucose oxidase; Glucose Isomerase; Glutamate dehydrogenase; Glyceraldehyde-3-phosphate dehydrogenase; Hexokinase; Lactate Dehydrogenase; Malate dehydrogenase; PEP carboxylase; RNase A; Soybean trypsin inhibitor; Urease; Xanthine oxidase; Superoxide dismutase; Fibronectin; Restriction Endonucleases; Reverse transcriptase; M-MuLV; Monoclonal Antibodies; OKT3; HA-1A; BMA 031; CAMPATH-1; anti-TAC; Thrombopoietin; subtilisins; Bacillus thuringiensis crystal protein and the like.

CLAIMS:

14. The-process of claim 2, wherein the reconstitution stabilizer is a surfactant selected from the group consisting of pluronic, polyoxyethylene sorbitan mono-oleate, polyethylene mono-laureate, hydroxypropyl .beta.-cyclodextrin and N-actylglucoside.

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L22: Entry 10 of 11 File: USPT Apr 29, 1997

DOCUMENT-IDENTIFIER: US 5624898 A
TITLE: Method for administering neurologic agents to the brain

DATE FILED (1):
19941222

Brief Summary Text (6):
Neurotrophic and neuritogenic factors are agents that affect the survival and differentiation of neurons in the peripheral and central nervous systems. These growth promoting factors are signaling substances that are synthesized in tissues in response to neurons capable of responding to the factor. They bind to receptors on the surface of nerve cells to promote neuron survival and in some cases are incorporated into nerve cell membranes. Studies further indicate that nerve growth factor (NGF), a class of polypeptide signaling substances, may be capable of improving cholinergic functioning which would prevent injury-induced degeneration of basal forebrain cholinergic neurons and improve cognitive functioning. Nerve growth factor (NGF) is known to bind to receptors on axon terminals, and can be internalized and retrogradely transported to the cell body of neurons. See M. Seiler, Brain Res. 300:33-39 (1984). Other naturally-occurring nerve growth promoting factors include gangliosides, phosphatidylserine (PS), brain-derived neurotrophic factor, fibroblast growth factor, insulin, insulin-like growth factors, ciliary neurotrophic factor and glia-derived nexin.

Brief Summary Text (19):
The neurologic agent is the active ingredient of the composition. It is preferred that the neurologic agent promote nerve cell growth and survival or augment the activity of functioning cells. Among those agents that are preferred are neurotrophic and neuritogenic factors that are similar to naturally occurring nerve growth promoting substances. Among the preferred neurologic agents are gangliosides, phosphatylserine (PS), nerve growth factor (NGF), brain-derived neurotrophic factor, fibroblast growth factor, insulin, insulin-like growth factors, ciliary neurotrophic factor, glia-derived nexin, and cholinergic enhancing factors such as phosphoethanolamine and thyroid hormone T.3. GM-1 ganglioside and nerve growth factor (NGF) are particularly preferred. One or several neurologic substances may be combined together.

Detailed Description Text (4):
The neurologic agent that is administered by the method of the invention may be generally absorbed into the bloodstream and the neural pathway of the mammal. It is preferred that the agent exhibits minimal effects systemically. It is preferred that a large enough quantity of the agent be applied in non-toxic levels in order to provide an effective level of activity within the neural system against the brain disease. It is further preferred that the neurologic agent promote nerve cell growth and survival or augment the activity of functioning cells including enhancing the synthesis of neurotransmitter substances. Among those agents that are preferred are neurotrophic and neuritogenic factors that are similar to or the same as nerve growth promoting substances that are naturally occurring in the nervous system of a mammal. The agent may be administered to the nasal cavity alone or in combination with other neurologic agents. The agent may be combined with a carrier and/or other adjuvants to form a pharmaceutical composition. Among the preferred neurologic agents are gangliosides, nerve growth factor (NGF), phosphatidylserine (PS), brain-derived neurotrophic factor, fibroblast growth factor, insulin, insulin-like growth factors, ciliary neurotrophic factor, glia-derived nexin, and cholinergic enhancing factors such as phosphoethanolamine and thyroid hormone T.3. Among those agents that are particularly preferred are GM-1 ganglioside and nerve growth factor (NGF).

Detailed Description Text (13):
As in the foregoing methods of treatment, prophylactic therapies may apply the neurologic agent alone or in combination with a carrier, other neurologic agents, and/or other substances that may enhance the absorption of the agent into the olfactory neurons. Potential neurologic agents include gangliosides, nerve growth factor (NGF), phosphatidylserine (PS), brain-derived neurotrophic factor, fibroblast growth factor, insulin, insulin-like growth factors, ciliary neurotrophic factor, glia-derived nexin, and cholinergic enhancing factors such as phosphoethanolamine and thyroid hormone T.3. GM-1 ganglioside and nerve growth factor (NGF) are among those agents that are particularly preferred for prophylactic treatment of brain disorders.

Detailed Description Text (17):
The neurologic therapeutic agent of the pharmaceutical composition may be any substance that promotes the survival of neurons and prevents the further loss of nerve cells. It is preferred that the agent has minimal systemic effects and augments the activity of naturally occurring nerve growth promoting factors. Preferably, the agent acts as a nerve growth promoting factor to prevent degeneration of neurons to induce regrowth of dendrite and axons and to augment the function of remaining neurons such as synthesizing neurotransmitter substances. Among the neurologic agents that are preferred are nerve growth factor (NGF), gangliosides, phosphatidylserine (PS), brain-derived neurotrophic factor, fibroblast growth factor, insulin, insulin-like growth factors, ciliary neurotrophic factor, glia-derived nexin, and cholinergic enhancing factors such as phosphoethanolamine and thyroid hormone T.3.

Detailed Description Text (21):
A preferred embodiment of the pharmaceutical composition of the invention is a micellar suspension of GM-1 ganglioside with an effective amount of nerve growth factor (NGF) combined with appropriate amounts of a stabilizer such as microcrystalline cellulose, a suspending agent such as carboxymethyl cellulose or hydroxypropyl methylcellulose, an emulsifier such as polysorbate 80, a preservative such as benzalkonium chloride, an antimicrobial such as phenylethyl alcohol, and a thickener such as dextrose.

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L22: Entry 7 of 11 File: USPT Feb 22, 2000

DOCUMENT-IDENTIFIER: US 6028066 A
TITLE: Prodrugs comprising fluorinated amphiphiles

DATE FILED (1):
19970702

Brief Summary Text (107):
Peptides and peptide analogs, include, for example, manganese super oxide dismutase, tissue plasminogen activator (t-PA), glutathione, insulin, dopamine, peptide ligands containing RGD, AGD, RGE, KGD, KGE or KQAGDV (Peptides with affinity for the GPIIBIIIa receptor), opiate peptides, enkephalins, endorphins and their analogs, human chorionic gonadotropin (HCG), corticotropin release factor (CRF), cholecystokinins and their analogs, bradykinins and their analogs and promoters and inhibitors, elastins, vasopressins, pepsins, glucagon, substance P, integrins, captopril, enalapril, lisinopril and other ACE inhibitors, adrenocorticotropic hormone (ACTH), oxytocin, calcitonins, IgG or fragments thereof, IgA or fragments thereof, IgM or fragments thereof, ligands for Effector Cell Protease Receptors (all subtypes), thrombin, streptokinase, urokinase, t-PA and all active fragments or analogs, Protein Kinase C and its binding ligands, interferons (.alpha.-interferon, .beta.-interferon, .gamma.-interferon), colony stimulating factors (CSF), granulocyte colony stimulating factors (GCSF), granulocyte-macrophage colony stimulating factors (GM-CSF), tumor necrosis factors (TNF), nerve growth factors (NGF), platelet derived growth factors, lymphotoxin, epidermal growth factors, fibroblast growth factors, vascular endothelial cell growth factors, erythropoietin, transforming growth factors, oncostatin M, interleukins (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12), metalloprotein kinase ligands, collagenases and agonists and antagonists.

Brief Summary Text (161):
Exemplary lipids which may be used to prepare the stabilizing materials of the present invention include, for example, fatty acids, lysolipids, fluorinated lipids, phosphocholines, such as those associated with platelet activation factors (PAF) (Avanti Polar Lipids, Alabaster, Ala.), including 1-alkyl-2-acetoyl-sn-glycero 3-phosphocholines, and 1-alkyl-2-hydroxy-sn-glycero 3-phosphocholines, which target blood clots; phosphatidylcholine with both saturated and unsaturated lipids, including dioleoyphosphatidylcholine; dimyristoylphosphatidylcholine; dipentadecanoylphosphatidylcholine; dilauroylphosphatidylcholine; dipalmitoylphosphatidylcholine (DPPC); distearoylphosphatidylcholine (DSPC); and diarachidonylphosphatidylcholine (DAPC); phosphatidylethanolamines, such as dioleoylphosphatidylethanolamine, dipalmitoylphosphatidylethanolamine (DPPE) and distearoylphosphatidylethanolamine (DSPE); phosphatidylserine; phosphatidylglycerols, including distearoylphosphatidylglycerol (DSPG); phosphatidylinositol; sphingolipids such as sphingomyelin; glycolipids such as ganglioside GM1 and GM2; glucolipids; sulfatides; glycosphingolipids; phosphatidic acids, such as dipalmitoylphosphatidic acid (DPPA) and distearoylphosphatidic acid (DSPA); palmitic acid; stearic acid; arachidonic acid; oleic acid; lipids bearing polymers, such as chitin, hyaluronic acid, polyvinylpyrrolidone or polyethylene glycol (PEG), also referred to herein as "pegylated lipids" with preferred lipid bearing polymers including DPPE-PEG (DPPE-PEG), which refers to the lipid DPPE having a PEG polymer attached thereto, including, for example, DPPE-PEG5000, which refers to DPPE having attached thereto a PEG polymer having a mean average molecular weight of about 5000; lipids bearing sulfonated mono-, di-, oligo- or polysaccharides; cholesterol, cholesterol sulfate and cholesterol hemisuccinate; tocopherol hemisuccinate; lipids with ether and ester-linked fatty acids; polymerized lipids (a wide variety of which are well known in the art); diacetyl phosphate; dicetyl phosphate; stearylamine; cardiolipin; phospholipids with short chain fatty acids of about 6 to about 8 carbons in length; synthetic phospholipids with

asymmetric acyl chains, such as, for example, one acyl chain of about 6 carbons and another acyl chain of about 12 carbons; ceramides; non-ionic liposomes including niosomes such as polyoxyalkylene (e.g., polyoxyethylene) fatty acid esters, polyoxyalkylene (e.g., polyoxyethylene) fatty alcohols, polyoxyalkylene (e.g., polyoxyethylene) fatty alcohol ethers, polyoxyalkylene (e.g., polyoxyethylene) sorbitan fatty acid esters (such as, for example, the class of compounds referred to as TWEEN.RTM., including, for example, TWEEN.RTM. 20, TWEEN.RTM. 40 and TWEEN.RTM. 80, commercially available from ICI Americas, Inc., Wilmington, Del.), glycerol polyethylene glycol oxystearate, glycerol polyethylene glycol ricinoleate, alkyloxylated (e.g., ethoxylated) soybean sterols, alkyloxylated (e.g., ethoxylated) castor oil, polyoxyethylene-polyoxypropylene polymers, and polyoxyalkylene (e.g., polyoxyethylene) fatty acid stearates; sterol aliphatic acid esters including cholesterol sulfate, cholesterol butyrate, cholesterol isobutyrate, cholesterol palmitate, cholesterol stearate, lanosterol acetate, ergosterol palmitate, and phytosterol n-butyrate; sterol esters of sugar acids including cholesterol glucuronide, lanosterol glucuronide, 7-dehydrocholesterol glucuronide, ergosterol glucuronide, cholesterol gluconate, lanosterol gluconate, and ergosterol gluconate; esters of sugar acids and alcohols including lauryl glucuronide, stearoyl glucuronide, myristoyl glucuronide, lauryl gluconate, myristoyl gluconate, and stearoyl gluconate; esters of sugars and aliphatic acids including sucrose laurate, fructose laurate, sucrose palmitate, sucrose stearate, glucuronic acid, gluconic acid and polyuronic acid; saponins including sarsasapogenin, smilagenin, hederagenin, oleanolic acid, and digitoxigenin; glycerol dilaurate, glycerol trilaurate, glycerol dipalmitate, glycerol and glycerol esters including glycerol tripalmitate, glycerol distearate, glycerol tristearate, glycerol dimyristate, glycerol trimyristate; long chain alcohols including n-decyl alcohol, lauryl alcohol, myristyl alcohol, cetyl alcohol, and n-octadecyl alcohol; 6-(5-cholesten-3.beta.-yloxy)-1-thio-.beta.-D-galactopyranoside; digalactosyldiglyceride; 6-(5-cholesten-3.beta.-yloxy)-hexyl-6-amino-6-deoxy-1-thio-.beta.-D-galact opyranoside; 6-(5-cholesten-3.beta.-yloxy)hexyl-6-amino-6-deoxyl-1-thio-.alpha.-D-manno pyranoside; 12-(((7'-diethylaminocoumarin-3-yl)-carbonyl)methylamino)octadecanoic acid; N-[12-(((7'-diethylaminocoumarin-3-yl)-carbonyl)methylamino)octadeca noyl]-2-aminopalmitic acid; cholesteryl(4'-trimethyl-ammonio)butanoate; N-succinyldioleoylphosphatidylethanolamine; 1,2-dioleoylsn-glycerol; 1,2-dipalmitoyl-sn-3-succinylglycerol; 1,3-dipalmitoyl-2-succinylglycerol; 1-hexadecyl-2-palmitoylglycerophosphoethanolamine and palmitoylhomocysteine, and/or any combinations thereof In preferred embodiments, the stabilizing materials comprise phospholipids, including one or more of DPPC, DPPE, DPPA, DSPC, DSPE, DSPG, and DAPC.

Brief Summary Text (200):
The gas and/or gaseous precursor filled vesicles used in the present invention may be controlled according to size, solubility and heat stability by choosing from among the various additional or auxiliary stabilizing materials described herein. These materials can affect the parameters of the vesicles, especially vesicles formulated from lipids, not only by their physical interaction with the membranes, but also by their ability to modify the viscosity and surface tension of the surface of the gas and/or gaseous precursor filled vesicle. Accordingly, the gas and/or gaseous precursor filled vesicles used in the present invention may be favorably modified and further stabilized, for example, by the addition of one or more of a wide variety of (i) viscosity modifiers, including, for example, carbohydrates and their phosphorylated and sulfonated derivatives; polyethers, preferably with molecular weight ranges between 400 and 100,000; and di- and trihydroxy alkanes and their polymers, preferably with molecular weight ranges between 200 and 50,000; (ii) emulsifying and/or solubilizing agents including, for example, acacia, cholesterol, diethanolamine, glyceryl monostearate, lanolin alcohols, lecithin, mono- and di-glycerides, mono-ethanolarnine, oleic acid, oleyl alcohol, poloxamer, for example, poloxamer 188, poloxamer 184, and poloxamer 181, Pluronics.RTM. (BASF, Parsippany, N.J.), polyoxyethylene 50 stearate, polyoxyl 35 castor oil, polyoxyl 10 oleyl ether, polyoxyl 20 cetostearyl ether, polyoxyl 40 stearate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, propylene glycol diacetate, propylene glycol monostearate, sodium lauryl sulfate, sodium stearate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, stearic acid, trolamine, and emulsifying wax; (iii) suspending and/or viscosity-increasing agents, including, for example, acacia, agar, alginic acid, aluminum monostearate, bentonite, magma, carbomer 934P, carboxymethylcellulose, calcium and sodium and sodium 12, carrageenan, cellulose, dextran, gelatin, guar gum, locust bean gum, veegum, hydroxyethyl cellulose, hydroxypropyl methylcellulose, magnesium-aluminum-silicate, Zeolites.RTM., methylcellulose, pectin, polyethylene oxide, povidone, propylene glycol alginate, silicon dioxide, sodium alginate, tragacanth, xanthin gum, .alpha.-d-gluconolactone, glycerol and mannitol; (iv)

synthetic suspending agents, such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), polyvinylalcohol (PVA), polypropylene glycol (PPG), and polysorbate; and (v) tonicity raising agents which stabilize and add tonicity, including, for example, sorbitol, mannitol, trehalose, sucrose, propylene glycol and glycerol.

Brief Summary Text (224):
In connection with the targeting of endothelial cells, suitable targeting ligands include, for example, one or more of the following: growth factors, including, for example, basic fibroblast growth factor (bFGF), acidic fibroblast growth factor (aFGF), transforming growth factor-alpha (TGF-.alpha.), transforming growth factor-beta (TGF-.beta.), platelet-derived endothelial cell growth factor (PD-ECGF) vascular endothelial growth factor (VEGF) and human growth factor (HGF); angiogenin; tumor necrosis factors, including tumor necrosis factor-alpha (TNF-.alpha.) and tumor necrosis factor-beta (TNF-.beta.), and receptor antibodies and fragments thereof to tumor necrosis factor (TNF) receptor 1 or 2 family, including, for example, TNF-R1, TNF-R.sub.2, FAS, TNFR-RP, NGF-R, CD30, CD40, CD27, OX40 and 4-1BB; copper-containing polyribonucleotide angiotropin with a molecular weight of about 4,500, as well as low molecular weight non-peptide angiogenic factors, such as 1-butyryl glycerol; the prostaglandins, including, for example, prostaglandin E.sub.1 (PGE.sub.1) and prostaglandin E.sub.2 (PG.sub.2); nicotinamide; adenosine; dipyridamole; dobutamine; hyaluronic acid degradation products, such as, for example, degradation products resulting from hydrolysis of .beta. linkages, including hyalobiuronic acid; angiogenesis inhibitors, including, for example, collagenase inhibitors; minocycline; medroxyprogesterone; chitin chemically modified with 6-O-sulfate and 6-O-carboxymethyl groups; angiostatic steroids, such as tetrahydrocortisol; and heparin, including fragments of heparin, such as, for example, fragments having a molecular weight of about 6,000, admixed with steroids, such as, for example, cortisone or hydrocortisone; angiogenesis inhibitors, including angioinhibin (AGM-1470--an angiostatic antibiotic); platelet factor 4; protamine; sulfated polysaccharide peptidoglycan complexes derived from the bacterial wall of an Arthobacter species; fungal-derived angiogenesis inhibitors, such as fumagillin derived from Aspergillus fumigatus; D-penicillamine; gold thiomalate; thrombospondin; vitamin D.sub.3 analogues, including, for example, 1-.alpha.,25-dihydroxy vitamin D.sub.3 and a synthetic analogue 22-oxa-1-.alpha.,25-dihydroxy vitamin D.sub.3 ; interferons, including, for example, .alpha.-interferon, .beta.-interferon and .gamma.-interferon; cytokines and cytokine fragments, such as the interleukins, including, for example, interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-7 (IL-7) and interleukin-8 (IL-8); erythropoietin; a 20-mer peptide or smaller for binding to receptor or antagonists to native cytokines; granulocyte macrophage colony stimulating factor (GMCSF); LTB.sub.4 leukocyte receptor antagonists; analogues including low molecular weight fragments of heparin or analogues of heparin; simple sulfated polysaccharides, such as cyclodextrins, including .alpha.-, .beta.-and .gamma.-cyclodextrin; tetradecasulfate; transferrin; ferritin; platelet factor 4; protamine; Gly-His-Lys complexed to copper; ceruloplasmin; (12R)-hydroxyeicosatrienoic acid; okadaic acid; lectins; antibodies; CD11a/CD18; and Very Late Activation Integrin-4 (VLA-4).

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L22: Entry 6 of 11 File: USPT Sep 19, 2000

DOCUMENT-IDENTIFIER: US 6120751 A
TITLE: Charged lipids and uses for the same

DATE FILED (1):
19970908

Detailed Description Text (149):
their phosphorylated and sulfonal:ed derivatives; polyethers, preferably with molecular weight ranges between 400 and 100,000; and di- and trihydroxy alkanes and their polymers, preferably with molecular weight ranges between 200 and 50,000; (ii) emulsifying and/or solubilizing agents including, for example, acacia, cholesterol, diethanolamine, glyceryl monostearate, lanolin alcohols, lecithin, mono- and di-glycerides, mono-ethanolamine, oleic acid, oleyl alcohol, poloxamer, for example, poloxamer 188, poloxamer 184, and poloxamer 181, Pluronics.RTM. (BASF, Parsippany, N.J.), polyoxyethylene 50 stearate, polyoxyl 35 castor oil, polyoxl 10 oleyl ether, polyoxyl 20 cetostearyl ether, polyoxyl 40 stearate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, propylene glycol diacetate, propylene glycol monostearate, sodium lauryl sulfate, sodium stearate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, stearic acid, trolamine, and emulsifying wax; (iii) suspending and/or viscosity-increasing agents, including, for example, acacia, agar, alginic acid, aluminum monostearate, bentonite, magma, carbomer 934P, carboxymethylcellulose, calcium and sodium and sodium 12, carrageenan, cellulose, dextran, gelatin, guar gum, locust bean gum, veegum, hydroxyethyl cellulose, hydroxypropyl methylcellulose, magnesium-aluminum-silicate, Zeolites.RTM., methylcellulose, pectin, polyethylene oxide, povidone, propylene glycol alginate, silicon dioxide, sodium alginate, tragacanth, xanthin gum, .alpha.-d-gluconolactone, glycerol and mannitol; (iv) synthetic suspending agents, such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), polyvinylalcohol (PVA), polypropylene glycol (PPG), and polysorbate; and (v) tonicity raising agents which stabilize and add tonicity, including, for example, sorbitol, mannitol, trehalose, sucrose, propylene glycol and glycerol.

Detailed Description Text (182):
In connection with the targeting of endothelial cells, suitable targeting ligands include, for example, one or more of the following: growth factors, including, for example, basic fibroblast growth factor (bFGF), acidic fibroblast growth factor (aFGF), transforming growth factor-alpha (TGF-.alpha.), transforming growth factor-beta (TGF-.beta.), platelet-derived endothelial cell growth factor (PD-ECGF) vascular endothelial growth factor (VEGF) and human growth factor (HGF); angiogenin; tumor necrosis factors, including tumor necrosis factor-alpha (TNF-.alpha.) and tumor necrosis factor-beta (TNF-.beta.), and receptor antibodies and fragments thereof to tumor necrosis factor (TNF) receptor 1 or 2 family, including, for example, TNF-R1, TNF-R2, FAS, TNFR-RP, NGF-R, CD30, CD40, CD27, OX40 and 4-1BB; copper-containing polyribo-nucleotide angiotropin with a molecular weight of about 4,500, as well as low molecular weight non-peptide angiogenic factors, such as 1-butyryl glycerol; the prostaglandins, including, for example, prostaglandin E.sub.1 (PGE.sub.1) and prostaglandin E.sub.2 (PGE.sub.2); nicotinamide; adenosine; dipyridamole; dobutamine; hyaluronic acid degradation products, such as, for example, degradation products resulting from hydrolysis of .beta. linkages, including hyalobiuronic acid; angiogenesis inhibitors, including, for example, collagenase inhibitors; minocycline; medroxy-progesterone; chitin chemically modified with 6-O-sulfate and 6-O-carboxy-methyl groups; angiostatic steroids, such as tetrahydrocortisol; and heparin, including fragments of heparin, such as, for example, fragments having a molecular weight of about 6,000, admixed with steroids, such as, for example, cortisone or hydrocortisone; angiogenesis inhibitors, including angioinhibin (AGM-1470--an

angiostatic antibiotic); platelet factor 4; protamine; sulfated polysaccharide peptidoglycan complexes derived from the bacterial wall of an Arthobacter species; fungal-derived angiogenesis inhibitors, such as fumagillin derived from Aspergillus fumigatus; D-penicillamine; gold thiomalate; thrombospondin; vitamin D.sub.3 analogues, including, for example, 1-.alpha., 25-dihydroxyvitamin D.sub.3 and a synthetic analogue 22-oxa-1-.alpha., 25-dihydroxy-vitamin D.sub.3 ; interferons, including, for example, .alpha.-interferon, .beta.-interferon and .gamma.-interferon; cytokines and cytokine fragments, such as the interleukins, including, for example, interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-3 (IL-3), interleuikin-4 (IL-4), interleukin-5 (IL-5), interluekin-6 (IL-6), interleukin-7 (IL-7) and interleukin-8 (IL-8); erythropoietin; a 20-mer peptide or smaller for binding to receptor or antagonists to native cytokines; granulocyte macrophage colony stimulating factor (GMCSF); LTB.sub.4 leukocyte receptor antagonists; heparin, including low molecular weight fragments of heparin or analogues of heparin; simple sulfated polysaccharides, such as cyclodextrins, including .alpha.-cyclodextrin, .beta.-cyclodextrin, and .gamma.-cyclodextrin; tetradecasulfate; transferrin; ferritin; platelet factor 4; protamine; Gly-His-Lys complexed to copper; ceruloplasmin; (12R)-hydroxyeico-satrienoic acid; okadaic acid; lectins; antibodies; CD11a/CD18; and Very Late Activation Integrin-4 (VLA-4).

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L22: Entry 1 of 11 File: USPT Sep 17, 2002

DOCUMENT-IDENTIFIER: US 6451787 B1
TITLE: Remedies for ocular diseases

Priority Application Date (1):
19981013

Brief Summary Text (25):
The route of administration of the compounds can be either parenteral or oral. As dosage forms for parenteral administration, eye drop, injection, nose drop and the like can be mentioned whereas as for oral administration, tablet, capsule, powder and the like can be mentioned, all of which can be formulated using vehicles or additives as well as techniques routinely used in the art. For example, in the case of an eye drop, as the vehicles or additives, isotonizing agents such as sodium chloride, concentrated glycerin and the like, buffering agents such as sodium phosphate, sodium acetate and the like, surfactants such as polyoxyethylene sorbitan mono-oleate (it is referred to as Polysorbate 80 hereinafter), polyoxyl stearate 40, polyoxyethylene hydrogenated castor oil and the like, stabilization agents such as sodium citrate, sodium edetate and the like, as well as preservatives such as benzalkonium chloride, parabens and the like can be used when required to formulate the composition, and pH of the formulation should be within the range acceptable to ophthalmologic formulations with the range of pH 4-8 being preferable.

Other Reference Publication (12):
Unoki, K. et al., "Protection of the rat retina from ischemic injury by brain-derived neurotrophic factor, ciliary neurotrophic factor, and basic fibroblast growth factor", Invet Opht & Visual Sci, 1994, vol. 35, No. 3, pp 907-915.

WEST

Generate Collection | Print

L4: Entry 1 of 1266 File: USPT Nov 26, 2002

DOCUMENT-IDENTIFIER: US 6485725 B1
TITLE: Room temperature storable immunoglobulin preparation for intravenous injection

Brief Summary Text (46):
Examples of the stabilizer include monosaccharides (for example, glucose), disaccharides (for example, saccharose, maltose), sugar alcohols (for example, mannitol, sorbitol), neutral salts (for example, sodium chloride), amino acids (for example, glycine) and nonionic surfactants (for example, polyethylene glycol, polyoxyethylene-polyoxypropylene copolymer ("Pluronic", trade name), polyoxyethylene sorbitan fatty acid ester ("Tween", trade name)). The stabilizer is preferably added in an amount of about 1 to 10 w/v%.

Brief Summary Text (60):
Examples of the stabilizer include monosaccharides (for example, glucose) disaccharides (for example, saccharose, maltose), sugar alcohols (for example, mannitol, sorbitol), neutral salts (for example, sodium chloride), amino acids (for example, glycine), and nonionic surfactant (for example, polyethylene glycol, polyoxyethylene-polyoxypropylene copolymer ("Pluronic", trade name), polyoxyethylene sorbitan fatty acid ester ("Tween", trade name)). The stabilizer is preferably added in an amount of about 1 to 10 w/v%.

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L47: Entry 2 of 5 File: USPT Jul 4, 2000

DOCUMENT-IDENTIFIER: US 6083521 A
TITLE: Polymeric matrices and their uses in pharmaceutical compositions

Abstract Text (1):
This invention provides pharmaceutical compositions comprising polymeric matrices, especially those comprising IL-6 as an active ingredient. Specific novel poly(ethylene carbomate) polymers are also provided for more general use as matrix materials in sustained release compositions containing pharmacologically active compounds, as are methods of using of IL-6 for treatment of conditions mediated by IL-1 and/or TNF.alpha., e.g., certain autoimmune and inflammatory conditions, as well as septic shock.

Drawing Description Text (3):
FIG. 2 is a graph of the swelling of PEC implants in phosphate-buffered saline.

Detailed Description Text (11):
According to Makromol. Chem. 183, 2085-2092 (1982), especially page 2086, carbon dioxide epoxide polymers are considered to be biodegradable and it is said that preliminary results confirmed the biodegradability of carbon dioxide--ethylene oxide polymers and thus their use in controlled drug release. For support of the allegation regarding the biodegradability Jinko Zoki 3 (Suppl.), 212 (1974) was cited. In this publication it was said that poly(ethylene carbonate) belongs to the group of compounds which are most easily hydrolysed and even the enzyme pronase had no difficulty in decomposing it. This means that an enzymatic hydrolysis in vitro and in vivo would be possible, since pronase is composed of a mixture of hydrolytic enzymes. However, this comment seems very doubtful. We have subjected the poly(ethylene carbonate)s of our invention in the form of pressed disks of 5 mm diameter and 25 mg weight to 10 mg/ml pronase and 5 mM CaCl.sub.2.2H.sub.2 O in phosphate-buffered saline (PBS) of pH 7.4 and to 10 mg/ml pronase E and 5 mM CaCl.sub.2.2H.sub.2 O in phosphate-buffered saline of pH 7.4 (at 37.degree. C.) and no degradation could be observed (see FIG. 1). The pronase solution was renewed every day.

Detailed Description Text (23):
If the polymers of the invention are exposed to an aqueous medium, e.g. a phosphate-buffered saline of pH 7.4, practically no medium will be transported to their bulk part, e.g. as is seen from FIG. 2. Therefore no bulk erosion will occur and the remaining mass will be kept constant (100%) for a period of at least 28 days, e.g. as shown in the right graph of FIG. 3.

Detailed Description Text (84):
Another type of additive is a scavenger of the hydroxyl radical, possibly developed under the influence of the superoxide radical anion O.sub.2.sup.-, e.g. a polyol, especially a sugar alcohol, particularly mannitol. This additive was found to have also a favourable influence on body weight gain of test animals to which e.g. microencapsulated IL-3 is administered. Without this additive the body weight gain was delayed. When the composition is in the form of microparticles the same additive or another may be added externally to the existing microparticles, since it then has a favourable influence on the stability of a microparticle suspension--against flocculation and precipitation.

Detailed Description Text (158):
4 g PEC were dissolved in 80 ml of methylene chloride with magnetic stirring. To this solution an appropriate amount of IL-2 (113.2 mg for 2%, 11.32 mg for 0.2% etc.) dissolved in 6 ml of distilled water or water with some drops of ethanol was added. The mixture was intensively mixed with an Ultra-Turax to disperse the IL-2 solution in the

polymer phase (=inner W/O phase). 1 g of gelatin A was dissolved in 200 ml of 1/15 M phosphate buffer (pH 7.4) at 50.degree. C and the solution cooled down to 20.degree. C. (=outer W phase). The W/O- and the W-phase were intensively mixed. Thereby the inner W/O-phase was separated into small droplets which were dispersed homogenously in the outer W-phase. The resulting triple emulsion was slowly stirred for 1 hr. Hereby the methylene chloride was evaporated and the microparticles were hardened from the droplets of the inner phase.

Detailed Description Text (182):
4 g PEC are dissolved in 80 ml of methylene chloride with magnetic stirring. To this solution an appropriate amount of rhIL-6 (113.2 mg for 2%, 11.32 mg for 0.2% etc.) dissolved in 6 ml of distilled water or water with some drops of ethanol is added. The mixture is intensively mixed with an Ultra-Turax to disperse the IL-6 solution in the polymer phase (=inner W/O phase). 1 g of gelatin A is dissolved in 200 ml of 1/15 M phosphate buffer (pH 7.4) at 50.degree. C. and the solution cooled down to 20.degree. C. (=outer W phase). The W/O- and the W-phase are intensively mixed. Thereby the inner W/O-phase is separated into small droplets which were dispersed homogenously in the outer W-phase. The resulting triple emulsion is slowly stirred for 1 hr., the methylene chloride is evaporated, and the microparticles are hardened from the droplets of the inner phase.

CLAIMS:

10. A composition of claim 9, wherein the additive is a sugar alcohol.

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L64: Entry 58 of 61 File: USPT Nov 28, 1995

DOCUMENT-IDENTIFIER: US 5470582 A
TITLE: Controlled delivery of pharmaceuticals from preformed porous polymeric microparticles

DATE FILED (1):
19930205

Abstract Text (1):
A controlled release pharmaceutical composition comprising a physiologically active agent dispersed in preformed porous polymeric microparticles is provided. The active agent concentration may be up to about 10% by weight to achieve controlled release. Each of the porous microparticles has a plurality of preformed pores into which active agent is loaded and from which the active agent is subsequently released to the environment of use. The compositions are capable of delivering physiologically effective amounts of active agent for at least about thirty days, which delivery may be reversibly controlled by exposure to ultrasound.

Detailed Description Text (6):
By utilizing the method of the invention, it is possible to prepare pharmaceutical compositions suitable for parenteral administration which contain endogenous opioid agonists, such as encephalins and endorphins; hypothalamic hormones, such as gonadoliberin, melanostatin, melanoliberin, somatostatin, thyroliberin, substance P, and neurotensin; adenohypophyseal hormones, such as corticotropin, lipotropin, melanotropin, lutropin, thyrotropin, prolactin, and somatotropin; neurohypophyseal hormones; calcitropic (thyroid) hormones, such as parathyrin and calcitonin; thymic factors, such as thymosin, thymopoietin, circulating thymic factor, and thymic humoral factor; pancreatic hormones, such as insulin, glucagon and somatostatin; gastrointestinal hormones, such as gastrin, cholecystokinin, secretin, gastric inhibitory polypeptide, vasointestinal peptide, and motillin; chorionic (placental) hormones, such as choriogonadotropin and choriomammotropin; ovarian hormones, such as relaxin; vasoactive tissue hormones, such as angiotensin and bradykinin; growth and neurotrophic factors, such as nerve growth factor (NGF), ciliary neurotrophic factor (CNTF), brain derived neurotrophic factor (BDNF), glial derived neurotrophic factor (GDNF), epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF), tumor necrosis factor (TNF), and transforming growth factor (TGF), somatomedins and urogastrone; hemophilia factors, such as blood clotting factors VIII and IX; enzymes, such as streptokinase, fibrinolysin, deoxyribonuclease, and asparaginase; and artificial or pseudo peptides, such as deferoxamine. Many other classes and specific types of peptide and protein hormones and other biologically active molecules are known, such as the LHRH analogs, nafarelin, buserelin, leuprorelin, goserelin, deslorelin, gonadorelin, triptorelin, and histrelin. Peptide and protein hormones suitable for use in the present invention are disclosed in Johannes Meienhofer, "Peptide and Protein Hormones", in Burger's Medicinal Chemistry, 4th ed., (part II), Wolff, Ed., John Wiley and Sons (1979).

Detailed Description Text (11):
Suitable excipients, additives, and cryoprotectants include proteins, such as serum albumin; carbohydrates, including simple sugars such as mannitol and sucrose and polysaccharides such as dextran; lipids such as 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and 1,2-dipalmitoyl-sn-glycero-3-[phospho-rac-(1-glycerol)]sodium salt (DPPG), and mixtures thereof; and surfactants such as polysorbate 80 (Tween 80).

Detailed Description Text (23):
For example, an injectable formulation of the microparticles of this invention may be

dispersed in a suitable aqueous medium, optionally containing preservatives (e.g. methylparaben) and/or isotonizing agents (e.g. sodium chloride, sorbitol) or they may be suspended in an aqueous medium together with a vegetable oil (e.g. sesame oil). The dose of the controlled release composition of this invention and the selection of suitable adjuvants, carriers, and solvents will be affected by the contemplated end use and will vary depending upon the nature and amount of physiologically active agent in the microparticles, the dosage form, the desired duration of release, the recipient animal, and the purpose of the administration. A single dose of microparticles may be in the range of from about 0.01 mg to about 100 mg/kg of body weight.

Detailed Description Text (31):
In vitro release studies were performed by rotating a 50 mg sample of the microspheres in 10 mL of phosphate buffered saline (PBS, pH 7.4) (Vanderkamp.RTM. Sustained Release Apparatus, VanKel Industries, Inc.). The receiving fluid was periodically withdrawn and the study continued with fresh buffer. The amount of active agent released was quantified by measuring the radioactivity.

Detailed Description Text (50):
50 mg of loaded microspheres were sonicated and dissolved in 2 mL of 1:1 N-methylpyrrolidone/dimethylacetamide solution. A 100 .mu.L portion of this solution was added to 4 mL of acetonitrile and the mixture was made up to 10 mL with 0.1M pH 7 sodium phosphate. The polymer was precipitated by the addition of phosphate buffer. The solution was filtered through a disposable 0.45 .mu.m nylon 66 membrane filter. The filtrate, after discarding the first 2 mL, was assayed for nafarelin content by an isocratic reversed phase HPLC method using a C.sub.8 column. The mobile phase was 30% acetonitrile in 50 mM pH 3 sodium phosphate. The flow rate was set at 1 mL/min and the temperature was set at ambient.

Detailed Description Text (51):
The compositions of various loading solutions are summarized in Table I below. In experiments 1-3, different concentrations of nafarelin acetate were used, whereas in experiments 4-7 various excipients or additives such as dextran (mw 9300), Tween 80, and lipids were present.

Detailed Description Text (53):
The results from experiments 1-3 show a positive correlation between the loading level and the nafarelin concentration in the loading range between 2 and 100 mg/mL. Comparisons of experiments 2 and 6 and 1 and 7 indicate that Tween 80 and lipids (DPPC/DPPG) increase the loading.

Detailed Description Text (58):
100 mg of dry loaded microspheres of Example 6 were dispensed into a scintillation vial. 20 mL of fresh receiver fluid, 0.1M pH 7 sodium phosphate buffer containing 0.1% sodium azide, were added. The vial was closed with a Teflon cap equipped with a sampling port. The vial was then placed into a rack that was set into a tumbling motion. The apparatus was immersed in a constant temperature water bath at 37.degree. C. The entire volume in the vial was sampled at fixed intervals and replaced with fresh 20 mL portions of receiver fluid. The samples were assayed by an isocratic reversed phase HPLC method using a C.sub.8 column. The mobile phase was 30% acetonitrile in 50 mM pH 3 sodium phosphate. The flow rate was set at 1 mL/min and the temperature was set at ambient.

Detailed Description Text (62):
Experiments 1, 2, 6 and 7 (FIG. 7) show the effect of additives such as lipids (DPPC/DPPG) or Tween 80, a nonionic surfactant, on the release profile of nafarelin from the microspheres. The data suggest that both lipids (DPPC/DPPG) and surfactants retard the release of nafarelin and thus may be useful as rate-controlling excipients.

Detailed Description Text (65):
Following the procedures of Examples 1 and 6, preformed microparticles containing up to 5% nerve growth factor (NGF, MW.apprxeq.26,000) or ciliary neurotrophic factor (CNTF, MW.apprxeq.22,000) may be prepared. A 10 microgram sample of such particles may be introduced into a subject and is expected to release physiologically effective amounts of the active agent for several months.

Detailed Description Paragraph Table (1):
TABLE I ______________________________________ Compositions of Loading Solutions and Resulting Loading Levels of Nafarelin Acetate in Porous Preformed Polytactic Acid Microspheres Nafarelin Excipient/Additive Methanol Loading.sup.1 Exp. (mg/mL) (mg/mL)

(%) (%) (s.d.) ____ 1 100 -- 20 7.10 (0.16) 2 10 -- 20 2.43 (0.05) 3 2 -- 20 1.41 (0.05) 4 10 10 (dextran) 20 2.27 (0.13) 5 10 100 (dextran) 20 2.70 (0.09) 6 10 10 (Tween 80) 20 4.10 (0.11) 7 50 58:2 (DPPC:DPPG) 0 8.04 (0.05) ____ .sup.1 Numbers reported are means of three experiments with standard deviations (s.d.) in parentheses.

CLAIMS:

6. A composition of claim 5 wherein said neurotrophic factor is selected from the group consisting of brain derived neurotrophic factor, ciliary neurotrophic factor, fibroblast growth factor, glial derived neurotrophic factor, and nerve growth factor.

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L64: Entry 57 of 61 File: USPT Jan 9, 1996

DOCUMENT-IDENTIFIER: US 5482706 A
TITLE: Transmucosal therapeutic composition

DATE FILED (1):
19930416

Priority Application Date (1):
19920417

Abstract Text (1):
A transmucosal therapeutic composition comprising a physiologically active peptide or protein and a cytidine nucleotide derivative is described. The above composition results in a satisfactory transmucosal absorption of physiologically active peptides or proteins which are otherwise hardly absorbed from the mucosa. Since it allows self-administration to the mucosa, such as the nasal, vaginal or digestive tract mucosa, in lieu of injection which causes pain, the invention is of great utility as a pharmaceutical dosage form for physiologically active peptides or proteins which must be administered over a protracted time.

Detailed Description Text (10):
Monokines useful in the practice of the invention include interleukin-1, tumor necrosis factors (e.g. TNF-.alpha. and -.beta.), malignant leukocyte inhibitory factor (LIF) and so on.

Detailed Description Text (61):
In addition to the above two ingredients, the transmucosal therapeutic composition of the invention generally contains various pharmaceutically acceptable additives as well as a pharmaceutically acceptable carrier or base necessary for dispersion of such substances. Said additives include but are not limited to pH control agents, such as arginine, sodium hydroxide, glycine, hydrochloric acid, citric acid, etc., local anesthetics represented by benzyl alcohol, isotonizing agents such as sodium chloride, mannitol, sorbitol, etc., adsorption inhibitors such as Tween 80 etc., solubilizers such as cyclodextrins and derivatives thereof, stabilizers such as serum albumin etc., and reducing agents such as glutathione and so on.

Detailed Description Text (151):
In 155.5 .mu.l of 1/10M citrate buffer (pH 3.5) was dispersed 16.75 mg of human insulin (Wako Pure Chemical) and 50 .mu.l of this dispersion was blended with 50 .mu.l of physiological saline for injection (Comparative Preparation 9).

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L64: Entry 53 of 61 File: USPT May 19, 1998

DOCUMENT-IDENTIFIER: US 5753631 A
TITLE: Intercellular adhesion mediators

DATE FILED (1):
19950531

Abstract Text (1):
The present invention is directed towards compositions and methods for reducing or controlling inflammation and for treating inflammatory disease processes and other pathological conditions mediated by intercellular adhesion. The compositions of the invention include compounds that selectively bind selectin receptors, the selectin binding activity being mediated by a carbohydrate moiety. The selectin-binding moieties of the invention are derivatives of a sialylated, fucosylated N-acetyllactosamine unit of the Lewis X antigen. Compounds containing a selectin-binding moiety in both monovalent and multivalent forms are included in the invention. The compounds of the invention are provided as pharmaceutical compositions which include, for example, liposomes that carry selectin-binding moieties of the invention. The invention further includes immunoglobulins capable of selectively binding an oligosaccharide ligand that is recognized by a selectin receptor.

Detailed Description Text (118):
Preferably, the pharmaceutical compositions are administered intravenously. Thus, this invention provides compositions for intravenous administration which comprise a solution of the compound dissolved or suspended in a pharmaceutically acceptable carrier, preferably an aqueous carrier. A variety of aqueous carriers may be used, e.g., water, buffered water, 0.4% saline, and the like. These compositions may be sterilized by conventional, well known sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous solution prior to administration. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as pH adjusting and buffering agents, tonicity adjusting agents, wetting agents and the like, for example, sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, sorbitan monolaurate, triethanolamine oleate, etc.

Detailed Description Text (122):
For aerosol administration, the compounds are preferably supplied in finely divided form along with a surfactant and propellant. Typical percentages of SLe.sup.x oligosaccharide ligands or mimetics are 0.05%-30% by weight, preferably 1%-10%. The surfactant must, of course, be nontoxic, and preferably be soluble in the propellant. Representative of such agents are the esters or partial esters of fatty acids containing from 6 to 22 carbon atoms, such as caproic, octanoic, lauric, palmitic, stearic, linoleic, linolenic, olesteric and oleic acids with an aliphatic polyhydric alcohol or its cyclic anhydride such as, for example, ethylene glycol, glycerol, erythritol, arabitol, mannitol, sorbitol, the hexitol anhydrides derived from sorbitol, and the polyoxyethylene and polyoxypropylene derivatives of these esters. Mixed esters, such as mixed or natural glycerides may be employed. The surfactant may constitute 0.1%-20% by weight of the composition, preferably 0.25-5%. The balance of the composition is ordinarily propellant. Liquefied propellants are typically gases at ambient conditions, and are condensed under pressure. Among suitable liquefied propellants are the lower alkanes containing up to 5 carbons, such as butane and propane; and preferably fluorinated or fluorochlorinated alkanes. Mixtures of the above may also be employed. In producing the aerosol, a container equipped with a suitable valve is filled with the appropriate propellant, containing the finely divided compounds and surfactant. The ingredients are thus maintained at an elevated pressure

until released by action of the valve.

Detailed Description Text (284):
Liposomes were prepared by adding 12 .mu.l of absolute ethanol (ETOH) to each tube, warming briefly in a 50.degree. C. water bath and sonicating for 2 min. 238 .mu.l of warm phosphate buffered saline (PBS) was added slowly to each tube while sonicating and sonication was continued for a further 10 min. The final concentration of stock liposomes was 400 .mu.g glycolipids/ml in 5% ETOH/PBS.

Detailed Description Text (294):
9. All of the medium was removed from the wells and 50 .mu.l of solubilization buffer was added. This consisted of citrate buffer (24.3 ml of 0.1M Citric acid, 10.5 g/500 ml+25.7 ml of 0.2M dibasic sodium phosphate, 14.2 g/500 ml and SQ H.sub.2 O to 100 ml) containing 0.1% NP-40 detergent.

Detailed Description Text (295):
10. The plate was incubated on a rotary shaker for 10 min and then 0.05 ml of OPDA solution [8 mg o-phenylene-diamine, Sigma cat# P-1526, 8 .mu.l of 30% H.sub.2 O.sub.2 and 10 ml of citrate buffer (as above)] was added to each well. The reaction was allowed to develop for 15 min and then 25 .mu.l of 4N H.sub.2 SO.sub.4 was added to each well to stop the reaction.

Detailed Description Text (305):
Enzyme treatment of the HL60 cells was carried out as follows: 12.4.times.10.sup.6 cells were washed twice with Hanks Balanced Salt Solution containing 20 mM HEPES and 0.2% glucose, followed by a single wash step in normal saline. The endo-.beta.-galactosidase (0.1 Unit, ICN Chemicals, Inc., Irvine, Calif.) was dissolved in 200 .mu.l normal saline and 200 .mu.l sodium acetate buffer, pH 6.01. 200 .mu.l (containing 0.05 U of enzyme) was added to 3.times.10.sup.6 HL60 cells, and 200 .mu.l of the acetate buffer was added to a similar number of cells to be used as the buffer control. Both tubes were incubated at 37.degree. C. for 60 min. with gentle shaking. The tubes were then cooled in ice and the cells were washed three times in HBSS containing HEPES and glucose and were then counted and suspended to 2.times.10.sup.6 /ml.

Detailed Description Text (425):
Microflex III 96 well ELISA plates were coated with 50 .mu.L of recombinant E-selectin (4 .mu.g/mL) in Dulbecco's phosphate buffered saline (DPBS) and incubated at room temperature for 3 hours. The plates were then washed three times with 200 .mu.L DPBS containing bovine serum albumin (10 mg/mL: DPBS-BSA) and incubated at room temperature for 60 minutes with DPBS-BSA.

Detailed Description Text (451):
Animals were dosed with different oligosaccharide preparations or phosphate buffered saline (PBS) five minutes before administration of cobra venom factor (20 units/Kg, i.v.). Included in this material was an aliquot of .sup.125 I-bovine serum albumin (0.5 .mu.Ci) and .sup.51 Cr labelled autologous red blood cells (0.5 .mu.Ci) for measuring plasma extravasation and hemorrhage respectively. Thirty minutes after administration of the cobra venom factor the animals were anesthetized with ketamine hydrochloride (10 mg/Kg) and exsanguinated via the posterior vena cava. The lung vasculature was then perfused through the right cardiac ventricle with 10 mL of PBS. The lungs were removed and the amount of radioactivity remaining within the tissue assessed with a gamma scintillation counter. Increased pulmonary vascular permeability was measured as the ratio of .sup.125 I in lung tissue compared with the amount present in 1 mL of venous blood obtained at the time of death. Lung hemorrhage was measured as the ratio of .sup.51 Cr in lung tissue compared with the amount present in 1 mL of venous blood obtained at the time of death. Neutrophil accumulation in lungs was determined by measuring the myeloperoxidase activity of lungs homogenized in PBS. Myeloperoxidase activity in lung supernatants was assayed by measuring the change in absorbance at 460 nm resulting from decomposition of H.sub.2 O.sub.2 in the presence of o-dianisidine

Detailed Description Text (453):
Preliminary experiments compared the activity of the SLe.sup.x analog, NeuAc.alpha.2,3Gal,.beta.1 4(Fuc.alpha.1,3)GlcNAc-OH (SLX-OH) with its nonfucosylated form, sialyl-N-acetyllactosamine (SLN-OH), as inhibitors of lung injury following injection of CVF. The positive controls (injected intravenously with CVF in phosphate buffered saline, PBS) showed (FIG. 16) a six-fold increase in lung permeability (frame A), a five-fold increase in hemorrhage (frame B) and a five-fold increase in lung myeloperoxidase (MPO) content (frame C) compared with negative controls not

administered CVF. When 200 .mu.g of SLN-OH (a control carbohydrate which does not support P-selectin mediated adhesion) was injected prior to CVF. the permeability. hemorrhage and MPO values were unaltered at 30 minutes, whereas treatment with SLX-OH reduced the permeability value by 43% (P<0.001), hemorrhage by 41% (P<0.004) and MPO content by 35% (P<0.006).

Other Reference Publication (28):
Leeuwenberg, Jet F.M., et al., "IFN-.gamma. Regulates the Expression of the Adhesion Molecule Elam-1 and IL-6 Production by Human Endothelial Cells In Vitro", Journal of Immunology, 145:2110-2114 (1990).

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L64: Entry 52 of 61 File: USPT Jun 9, 1998

DOCUMENT-IDENTIFIER: US 5762921 A
TITLE: Composition and methods for the treatment of tumors

DATE FILED (1):
19960130

Abstract Text (1):
The invention concerns a method for inducing a selective collapse of the vasculature of a solid tumor by administering to a patient a therapeutically effective dose of a combination of a compound preventing the formation of a functional thrombin-thrombomodulin complex and a cytokine selected from the group of TNF-.beta. (LT), TNF-.alpha., IL-1, and IFN-.gamma.. The invention further concerns the composition used in this method.

Detailed Description Text (25):
"Cytokine" is a generic term for proteins released by one cell population which act on another cell as intercellular mediators. Included among the cytokines are native tumor necrosis factor-.alpha. and -.beta. (TNF-.alpha. and -.beta.), interferons (IFNs) such as, IFN-.alpha., IFN-.beta. and IFN-.gamma., interleukins (ILs) such as, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, etc., growth hormones (GHs), including human growth hormone (hGH), N-methionyl hGH; and bovine GH; insulin-like growth factors, parathyroid hormone, thyroxine, insulin, proinsulin, relaxin, prorelaxin, glycoprotein hormones such as, follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH), hemopoietic growth factor, HGF, fibroblast growth factor, prolactin, placental lactogen, mullerian inhibiting substance, mouse gonadotropin-associated peptide, inhibin, activin, vascular endothelial growth factor, integrin, thrombopoietin, nerve growth factors, such as NGF-.beta., PDGF, transforming growth factors (TGFs) such as, TGF-.alpha. and TGF-.beta., insulin-like growth factor-1 and -2 (IGF-1 and IGF-2), erythropoietin, osteoinductive factors, colony stimulatina factors (CSFS) such as, M-CSF, GM-CSF, and G-CSF, and other polypeptide factors of any human and non-human animal species, and functional derivatives of such native proteins. The cytokines useful in the compositions and methods of the present invention are characterized by exhibiting one or more of the following properties stimulation of procoagulant activity, stimulation of natural killer (NK) and lymphokine-activated killer cell-mediated cytotoxicity, macrophage activation, stimulation of Fc receptor expression on mononuclear cells and antibody-dependent cellular cytotoxicity (ADCC), and enhancement of HLA class II antigen expression. Preferably, the cytokines to be used in accordance with the present invention should have the ability to stimulate procoagulant activity. Particularly referred cytokines are native TNF-.alpha. and -.beta., interleukin-1 and -2, interferon-.gamma., alone or in combination, and functional derivatives of these native proteins.

Detailed Description Text (108):
As mentioned before, the administration of the procoagulant or and the cytokine or inducer of cytokine production may be simultaneous or consecutive, with either agent being administered first. Similarly, the thrombomodulin inhibitor and the cytokine or cytokine inducer may be administered simultaneously or consecutively, in either order. Each agent can be formulated in the same or two separate pharmaceutical compositions. Therapeutic formulations are prepared for storage by mixing the active ingredient having the desired degree of purity with optional physiologically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than

about 10 residues) polypeptides; proteins, such as serum albumin, gelatin or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone, amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as Tween, Pluronics or PEG.

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L64: Entry 50 of 61 File: USPT Oct 20, 1998

DOCUMENT-IDENTIFIER: US 5824784 A
TITLE: N-terminally chemically modified protein compositions and methods

DATE FILED (1):
19941012

Abstract Text (1):
Provided herein are methods and compositions relating to the attachment of water soluble polymers to proteins. Provided are novel methods for N-terminally modifying proteins or analogs thereof, and resultant compositions, including novel N-terminally chemically modified G-CSF compositions and related methods of preparation. Also provided is chemically modified consensus interferon.

Brief Summary Text (12):
Another example is pegylated IL-6, EP 0 442 724, entitled, "Modified hIL-6," (see U.S. Pat. No. 5,264,209) which discloses polyethylene glycol molecules added to IL-6.

Detailed Description Text (31):
In yet another aspect of the present invention, provided are pharmaceutical compositions of the above. Such pharmaceutical compositions may be for administration for injection, or for oral, pulmonary, nasal or other forms of administration. In general, comprehended by the invention are pharmaceutical compositions comprising effective amounts of monopolymer/protein conjugate products of the invention together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions include diluents of various buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength; additives such as detergents and solubilizing agents (e.g., Tween 80, Polysorbate 80), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimersol, benzyl alcohol) and bulking substances (e.g., lactose, mannitol); incorporation of the material into particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc. or into liposomes. Such compositions may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the present N-terminally chemically modified proteins. See, e.g., Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, PA 18042) pages 1435-1712 which are herein incorporated by reference.

Detailed Description Text (42):
The three forms of monopegylated rh-G-CSF were separated from each other using ion exchange chromatography. The reaction mixture was loaded (1 mg protein/ml resin) onto a Pharmacia S SEPHAROSE FF column (Pharmacia XK50/30 reservoir, bed volume of 440 ml) equilibrated in buffer A (20 mM sodium acetate, pH 4.0). The column was washed with 3 column volumes of buffer A. The protein was eluted using a linear gradient from 0-23% buffer B (20 mM sodium acetate, pH 4.0, 1M NaCl) in 15 column volumes. The column was then washed with one column volume of 100% buffer B and reequilibrated with 3 column volumes of buffer A. The flow rate for the entire run was maintained at 8 ml/min. The eluent was monitored at 280 nm and 5 ml fractions were collected. Fractions containing the individual monopegylated species were pooled according to FIG. 1A. These pools were concentrated with a 350 mL Amicon stirred cell using a YM10 76 mm membrane.

Detailed Description Text (60):
In addition, stability studies were performed on the N-terminal and Lys-35 monopegylated species as prepared above. (The Lys-41 material was not used as it demonstrated no additional activity beyond unmodified G-CSF). These studies demonstrate that the N-terminally pegylated G-CSF is unexpectedly more stable upon storage than the other form of monopegylated G-CSF, monopegylated lysine 35. Stability was assessed in

terms of breakdown of product, as visualized using SEC-HPLC. Methods: N-terminally pegylated G-CSF and lysine-35 monopegylated G-CSF were studied in two pH levels, pH 4.0 and pH 6.0 at 4.degree. C., each for up to 16 days. Elevating the pH to 6.0 provides an environment for accelerated stability assays. For the pH 6.0 samples, N-terminal monopegylated G-CSF and Lysine 35 monopegylated G-CSF as prepared above were placed in a buffer containing 20 mM sodium phosphate, 5 mM sodium acetate, 2.5 % mannitol, 0.005 % TWEEN-80, pH 6.0 at a final protein concentration of 0.25 mg/ml. One ml aliquots were stored in 3 ml sterile injection vials. Vials of each was stored at 4.degree. C. and 29.degree. C. for up to 16 days. Stability was assessed by SEC-HPLC tracings. If the later measurements stayed the same (as ascertained by visual inspection) as the initial (Time=0) measurements, the sample was considered to be stable for that length of time. Results: Results are illustrated in FIGS. 6A-6C. (a) Comparison at pH 6.0 at 4.degree. C. FIG. 6A shows the 4.degree. C. SEC-HPLC profiles for N-terminally monopegylated G-CSF at pH 6 over time and FIG. 6B shows the 4.degree. C. SEC-HPLC profiles for lysine-35 monopegylated G-CSF at pH 6 over time. One interpretation is that the Lys-35 material is breaking down to a material with a molecular weight similar to that of unmodified G-CSF. (b) Extended duration at pH 4.0 at 4.degree. C. PH 4.0 and 4.degree. C. provides something of a control illustrating relatively stable conditions in that the N-terminal species shows no degradation. For the Lys 35 species, the break down of the material is still occurring, but at a much slower rate. (c) Comparison at pH 6.0 at 4.degree. C. FIGS. 6C illustrates the SEC-HPLC profiles for the monopegylated G-CSF's under these conditions, under extended time periods. As can be seen, at pH 6.0 and 4.degree. C., the lysine-35 material exhibits no increase in depegylation at day 16 or day 35 beyond what was seen for day 6 (FIG. 6B). This indicates that depegylation (instability) does not change, under those conditions, beyond day 6.

Detailed Description Text (69):
The mono-MPEG-GCSF derivative was purified by ion exchange chromatography using HiLoad 16/10 S SEPHAROSE HP column (Pharmacia) equilibrated with 20 mM sodium acetate buffer, pH 4. The reaction mixture was loaded on the column at a flow rate of 1 ml/min and the unreacted MPEG aldehyde eluted with three column volumes of the same buffer. Then a linear 400 minute gradient from 0% to 45% 20 mM sodium acetate, pH 4, containing 1M NaCl was used to the elute the protein-polymer conjugate at 4.degree. C.

Detailed Description Text (81):
Methods: Both N-terminally pegylated G-CSF samples were in 10 mM NaOac pH4.0 with 5% sorbitol, at a concentration of 1 mg protein/ml. The G-CSF's were pegylated with PEG 6000 for each. The amide-linked conjugate was prepared as in Example 1, and the amine linked conjugate was prepared as in Example 2. Six samples of each were stored for eight weeks at 45.degree. C. At the end of eight weeks, the degree of aggregation was determined using size exclusion chromatography and ion exchange chromatography.

Detailed Description Text (92):
At the 10 hour time point, the reaction mixture was diluted 5 times with water and the mono-MPEG-IFN-Con.sub.1 derivative was purified by ion exchange chromatography using HiLoad 16/10 S SEPHAROSE HP column (Pharmacia) equilibrated with 20 mM sodium acetate buffer, pH 4.0. The reaction mixture was loaded on the column at a flow rate of 1 ml/min and the unreacted MPEG aldehyde eluted with three column volumes of the same buffer. Then a linear 420 minute gradient from 0% to 75% of 20 mM sodium acetate, pH 4.0, containing 1M NaCl was used to the elute the protein-polymer conjugate at 4.degree. C.

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L64: Entry 17 of 61 File: USPT May 1, 2001

DOCUMENT-IDENTIFIER: US 6225282 B1
TITLE: Treatment of hearing impairments

DATE FILED (1):
19970102

Abstract Text (1):
Compositions and methods are provided for prophylactic or therapeutic treatment of a mammal for hearing impairments involving neuronal damage, loss, or degeneration, preferably of spinal ganglion neurons, by administration of a therapeutically effective amount of a trkB or trkC agonist, particularly a neurotrophin, more preferably NT-4/5. Also provided are improved compositions and methods for treatments requiring administration of a pharmaceutical having an ototoxic side-effect, wherein the improvement includes administering a therapeutically effective amount of a trkB or trkC agonist to treat the ototoxicity.

Detailed Description Text (31):
Agonists to trkB or trkC can be prepared by using the known family of ligands for trkB or trkC. Survival of developing sensory neurons is dependent upon trophic factors derived from their target tissues (Davies et al., 1986). Generally, a neurotrophin is a protein involved in the development, regulation and maintenance of the nervous system, and in particular of neurons. Currently, there are at least five known important neurotrophic factors: nerve growth factor (NGF), neurotrophin-3 (NT-3), neurotrophin-4 (NT-4/5, also sometimes called neurotrophin-5 (NT-5) or NT-4/5), brain-derived neurotrophic factor (BDNF), and ciliary neurotrophic factor (CNTF). The best characterized mammalian neurotrophic factors are members of the nerve growth factor (NGF) family of proteins, and are called neurotrophins. These include NGF (Levi-Montalcini, 1987), brain-derived neurotrophic factor (BDNF) (Barde et al., 1982; Leibrock et al., Nature (1989) 341:149) neurotrophin-3 (NT-3) (Hohn et al., Nature, 344: 339 (1990); Maisonpierre et al., Science, 247: 1446 (1990); Rosenthal et al., Neuron, 4: 767 (1990); copending U.S. Ser. No. 07/494,024 filed Mar. 15, 1990; U.S. application Ser. No. 07/490,004, filed Mar. 7, 1990; Emfors et al., 1990; Jones and Reichardt, 1990) and neurotrophin-4/5 (NT-4/5) (Berkemeier et al., 1991; Ip et al., 1992) and neurotrophin-6 (NT-6). While NT-6 is newly cloned from Xenopus (Gotz et al., 1994) and is less well understood, it is now well accepted that the other four mammalian neurotrophins exert their biological functions through activation of high-affinity binding receptors, the trks (Barbacid, 1993; Snider, 1994). Each of the neurotrophins binds to specific high-affinity receptors, the trks (Klein et al., 1990; Kaplan et al., 1991; Klein et al., 1991a; Klein et al., 1991b; Soppet et al., 1991; Squinto et al., 1991; Lamballe et al., 1991; Tsoulfas et al., 1993; Ip et al., 1993). For example, NGF selectively binds to trkA, BDNF and NT-4/5 to trkB, and NT-3 to trkC. Although neurotrophins exert their main effects through binding to the trks, they also bind to the NGF low affinity receptor, P75. Recent studies indicate that the binding of NGF to P75 may enhance the trkA-mediated signal transduction pathway (Davies et al., 1993a; Verdi et al., 1994; Barker and Shooter, 1994; Clary and Reichardt, 1994).

Detailed Description Text (38):
NT4/5 nucleic acid is defined as RNA or DNA which encodes a NT-4/5 polypeptide or which hybridizes to such DNA and remains stably bound to it under stringent conditions and is greater than about 10 bases in length; provided, however, that such hybridizing nucleic acid is novel and unobvious over any prior art nucleic acid including that which encodes or is complementary to nucleic acid encoding BDNF, NT-3, or NGF. Stringent conditions are those which (1) employ low ionic strength and high temperature for washing, for example, 0.15 M NaCl/0.015 M sodium citrate/0.1% NaDodSO.sub.4 at 50.degree. C., or (2) use during washing a denaturing agent such as formamide, for

example, 50% (vol/vol) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50 mM sodium phosphate buffer at pH 6.5 with 750 mM NaCl, 75 mM sodium citrate at 42.degree. C.

Detailed Description Text (129):
Therapeutic formulations of agonist(s) (and optionally ototoxic pharmaceutical drug) for treating hearing impairments are prepared for storage by mixing the agonist(s) or drug having the desired degree of purity with optional physiologically acceptable carriers, excipients, or stabilizers (Remington's Pharmaceutical Sciences, 16th edition, Oslo, A., Ed., [1980]), in the form of lyophilized cake or aqueous solutions. Acceptable carriers, excipients, or stabilizers are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as Tween, Pluronics, or polyethylene glycol (PEG).

Detailed Description Text (167):
To determine whether SGNs make trkB protein, the high-affinity binding receptor for BDNF and NT-4/5, trkB immunohistochemistry was performed on cross sections of P5 spiral ganglion with a polyclonal antiserum against trkB extracellular domain. Dual-immunohistochemistry was performed on cross sections of the spiral ganglion with trkB, trkA, or P75 and neurofilament protein antibodies. Texas red microscopy was used to show the staining pattern of antibodies against trkB, trkA and P75, respectively. Fluorescent microscopy was used to show the immunostainings of neurofilament antibody (N52) in the same sections as for Texas red microscopy. The SGN tissue was immersed in 4% paraformaldehyde (0.1M phosphate buffer, pH7.4) for 1 hour. After the preparations were cryoprotected with a 30% sucrose solution, cross sections were cut on a cryostat. The sections were first blocked with a 10% normal goat serum in 1% Triton X-100 in phosphate buffered saline ("PBS") for 20 minutes and then incubated with a mixture of a monoclonal antibody (N52) against neurofilament 200 kD (Boehringer, 5 .mu.g/ml) and a rabbit antibody against extracellular trkB (anti-trkB.sub.23-36; 2ug/ml; Yan et al., 1994; Gao et al., 1995), a trkA antiserum, or a P75 antiserum in PBS containing 3% normal goat serum and 1% Triton X-100 overnight at 4.degree. C. FITC-conjugated goat anti-mouse and Texas red-conjugated goat anti-rabbit secondary antibodies (1:70-100; Cappel) were then used to reveal the double labeling pattern in the sections. For neurofilament immunohistochemistry on cochlear wholemounts, the preparations were incubated with primary antibody for 2 days at 4.degree. C. and then Texas red-conjugated goat anti-mouse antiserum (1:100; Cappel) was used to reveal the staining pattern. For neurofilament immunocytochemistry, SGN cultures were fixed in 4% paraformaldehyde (in 0.1M phosphate buffer, pH 7.4) for 30 minutes, washed in PBS (pH 7.4), and the immunostainings were performed with a biotinylated sheep anti-mouse secondary antibody and a streptavidin-horse radish peroxidase conjugate (1:200: Amersham Life Science) as described in Gao et al. (1995b).

Detailed Description Text (191):
Two days after treatment with ototoxins or co-treatment with ototoxins and neurotrophins (or other growth factors), the cochlear explant cultures were fixed in 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4) for 30 min, washed in PBS, and subjected to double histochemical staining of the cochlear explant cultures. After incubation with the monoclonal antibody N52 against neurofilament protein (200 kd) in 1% Triton X100 containing 3% normal goat serum ("NGS") for 2 days at 4.degree. C., the explants were incubated with a Texas red-conjugated goat anti-mouse secondary antibody (1:70; Cappel) at room temperature for 40 min. The preparations were then stained with FITC-conjugated phalloidin (0.5 .mu.g/ml; Sigma) for 45 min, washed in PBS and mounted in Fluoromount-G (Southern Biotechnology Associates, Birmingham, Ala.) which contains an anti-fading agent.

Detailed Description Text (324):
Windebank A J, Smith A G, Russell J W (1994) The effect of nerve growth factor, ciliary neurotrophic factor, and ACTH analogs on cisplatin neurotoxicity in vitro. Neurology 44: 488-494.

Other Reference Publication (117):
Windebank et al., "The Effect of Nerve Growth Factor, Ciliary Neurotrophic Factor, and

ACTH Analogs on Cisplatin Neurotoxicity in vitro" Neurology 44:488-494 (Mar. 1994).

WEST Search History

DATE: Friday, December 06, 2002

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L64	l63 not l52	61	L64
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L47	L41 and l40	5	L47
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L44	L43 and l42 and l41 and l40	3	L44
L43	L38 and l27	20	L43
L42	L38 and l23	37	L42
L41	L38 and l25	7	L41
L40	L38 and l26	42	L40
L39	L38 and (l27 or l28)	21	L39
L38	L36 or l35	71	L38

L37	L36 and l35	2	L37
L36	L34 and medicament$1[ti,ab]	2	L36
L35	L34 and composition$1[ti,ab]	71	L35
L34	L32[ti,ab]	267	L34
L33	L32[ti,clm]	723	L33
L32	l13 or l15 or l16	5381	L32
L31	L30[ti,clm]	1157	L31
L30	l12 or l15 or l16	8028	L30
L29	L23[clm]	14129	L29
L28	(nonionic or (non-ionic)) near surfactant$1	32478	L28
L27	(polyoxyethylene adj polyoxypropylene) or (polyoxyethylene?polyoxypropylene) or (polyoxyethylene adj sorbitan) polysorbate or pluronic or tween	34926	L27
L26	(acetate or citrate or phosphate) with buffer$3	72467	L26
L25	((polyhydric or sugar) adj alcohol$1) or sorbitol or glucitol or manitol	70731	L25
L24	(polyhydric or sugar) adj alcohol$1	34790	L24
L23	monosaccharide$1 or disaccharide$1 or glucose or sucrose or fructose or mannose or saccharose or maltose	112037	L23
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L20	L19 and @ad<19981126	9	L20
L19	L18 or l17	16	L19
L18	L16 and l4	8	L18
L17	l15 and l4	12	L17
L16	Il6 or Il11 or (il adj (6 or 11))	3842	L16
L15	(cardiotrophin$1 or (interleukin adj (6 or 11)) or oncostatin or (ciliary adj neurotrophic adj factor))	2611	L15
L14	L13 and l4	1	L14
L13	(D adj factor) or ((leukemia or leukaemia) adj inhibit$3 adj factor)	986	L13
L12	lif or (D adj factor) or ((leukemia or leukaemia) adj inhibit$3 adj factor)	3813	L12
L11	lif or (D adj factor) or (leukemia inhibit$3 adj factor)	3806	L11
L10	L1 and (polyethylene adj glycol)	20490	L10
L9	L1 and (polyethylene adj glyco)	17	L9
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L7	L5 and @ad<19981126	172	L7
L6	L5 and @ad<1999	0	L6
L5	L4 and l3	192	L5

L4	l1 with stabiliz$5	1266	L4
L3	L2 and composition[clm]	3330	L3
L2	L1[clm]	6189	L2
L1	(polysorbate or polyoxyethylene or polyoxypropylene)	52379	L1

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